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Behcet's Syndrome: Case Report and Literature Review

K. V. Venkatasubramaniam, MD* and Douglas R. Swinehart, MD**

Behcet's syndrome is a disease commonly found in Japan and in countries around the Mediterranean Sea. In the U.S., it is relatively uncommon. This report describes a 24-year-old Lebanese-American man with Behcet's syndrome who

presented with symptoms four months after he developed arthritis and who had been initially diagnosed as having incomplete Reiter's syndrome. A literature review is included.

In 1937, a Turkish dermatologist, Hulusi Behcet, described a triple syndrome consisting of recurrent, painful oral and genital ulcers and recurrent ulcers of the eye. His original description was based upon an examination of three patients (1). The syndrome is now recognized as a multi-systemic disorder with mucocutaneous, ocular, intestinal, articular, vascular, urogenital, and neurological involvement (2,3), and it is classified with other mucocutaneous-ocular syndromes, e.g., erythema multiforme and Reiter's syndrome (4). The etiology remains unknown. No specific diagnostic or therapeutic aid is known. The disease is common in Japan and in the countries surrounding the Mediterranean Sea, such as Turkey, Italy, Greece, Israel, Lebanon, and other Arab lands. A few patients with this syndrome have been diagnosed recently in England and Germany. However, Behcet's syndrome is still an uncommon disease in the U.S. (5). This paper includes a report on a Lebanese-American patient with Behcet's syndrome and a complete literature review.

Epidemiology

In Japan, the number of patients with Behcet's syndrome has increased dramatically since World War II. In 1972-73, a nationwide survey yielded an estimated 7000-8500 pa-

tients, for a prevalence rate of 0.67:1,000 persons (6,7). More patients were found in the colder, northern parts of Japan (6,7). This prevalence rate is about ten times greater than that of northern England, where a survey done at Yorkshire found 32 patients in a population of five million (8). In the U.S., the prevalence rate for Olmstead County, Minnesota was 1:300,000 persons (9). Current estimates in Japan place the number of patients with Behcet's syndrome at 11,000 (9). Interestingly, while the syndrome has been found in Hawaii, none of the diagnosed patients were Japanese or Japanese-Americans, despite the frequency of the disease in Japan and the large Japanese population in Hawaii (10,11).

Historical Background

The earliest description of Behcet's syndrome as an acute endemic disease can be found in the writings of Hippocrates (12). Shigeta (1924), Adamantiadis (1931), and White-well (1934) described cases similar to Behcet's syndrome which preceded Behcet's classic paper in 1937 (1,13-15), from which the presently accepted name derives. Some have used the terms complete, abortive, partial, or incomplete to describe the clinical patterns of Behcet's syndrome (9), and Lehner has suggested dividing it into two major categories, the mucocutaneous or benign type and the neuro-ocular type, which may have more serious consequences (16).

Diagnostic Criteria

The Behcet's Disease Research Committee of Japan (1972) developed diagnostic criteria (Table I) which are more useful for classification than for clinical discrimination (17). The Committee proposed four major criteria for the diag-

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TABLE I
Diagnosis of Behcet's Syndrome

Major Criteria	Minor Criteria
1. Mouth (aphthous) Ulcers	1. Arthritis a. of major joints b. arthralgias
2. Iritis (with hypopyon)	2. Vascular Disease a. migratory superficial phlebitis b. major vessel thrombosis c. aneurysms d. peripheral gangrene e. retinal and vitreous hemorrhage, papilledema
3. Genital Ulcers	3. Central Nervous System Disease a. brain stem syndrome b. meningomyelitis c. confusional states
4. Skin Lesions a. pyoderma b. nodose lesions	4. Gastrointestinal Disease a. malabsorption b. colonic ulcers c. dilated intestinal loops
	5. Epididymitis

nosis of the complete syndrome, whereas articular, gastrointestinal, vascular, and nervous system involvement are considered minor criteria because they are less frequent (Table I). More recently, epididymitis and symptoms related to other organ systems have also been added to this classification. The incomplete syndrome requires that three major criteria be present some of the time, that recurrent hypopyon, iritis, or retinitis occur, accompanied by one of the major criteria, or that at least one of two major criteria with some minor criterion be present with clinical suspicion of the disease. It is important to realize that the complete type is not necessarily more severe than the incomplete (17).

Case Report

A 24-year-old native American-born Lebanese man experienced recurrent painful oral ulcerations for two years. About four months before his first visit to Henry Ford Hospital, he noted left knee pain with swelling and subsequently developed pain in the right knee, ankles, feet, elbows, and low back. An incorrect diagnosis of Reiter's syndrome was made. Although the mucocutaneous lesions were painful, the patient improved on 100 mg Indomethacin daily. He was referred to the Rheumatology Clinic of Henry Ford Hospital in August 1978 because he had arthralgia and painful skin ulcerations on the shaft of the penis and scrotum that had been unresponsive to neosporin ointment, parenteral penicillin, and smallpox

vaccine. His medical history revealed that he had had a bleeding duodenal ulcer four years earlier.

Examination revealed a thin man with normal vital signs who was in acute discomfort. On his face was a deep ulcer with an erythematous halo on the left cheek, a few erythematous macules on the palate, and a white pustule on an erythematous base on the lower lip (Fig. 1). There were nontender anterior cervical and inguinal lymph nodes bilaterally. A trace of effusion was noted in the left knee with good range of motion of all joints. Multiple painful ulcerations were present on the penis and scrotum with no evidence of balanitis (Fig. 2). His physical examination was otherwise normal.

Laboratory studies revealed a hemoglobin of 11 gms %, a mean corpuscular volume (MCV) of 80, total ironbinding capacity (TIBC) 276, and a serum iron of 60. The erythrocyte sedimentation rate (ESR) (Westergren) was 70 mm per hour. The reticulocyte count was 1.3%, rheumatoid factor negative, VDRL test nonreactive, and the HLA-B27 was positive. Urinalysis, serum multiphase screen, and chest x-ray were normal. The upper gastrointestinal x-rays revealed only a spastic duodenal bulb. X-rays of the knee, lumbosacral spine, and pelvis were normal, as was an ophthalmologic examination.

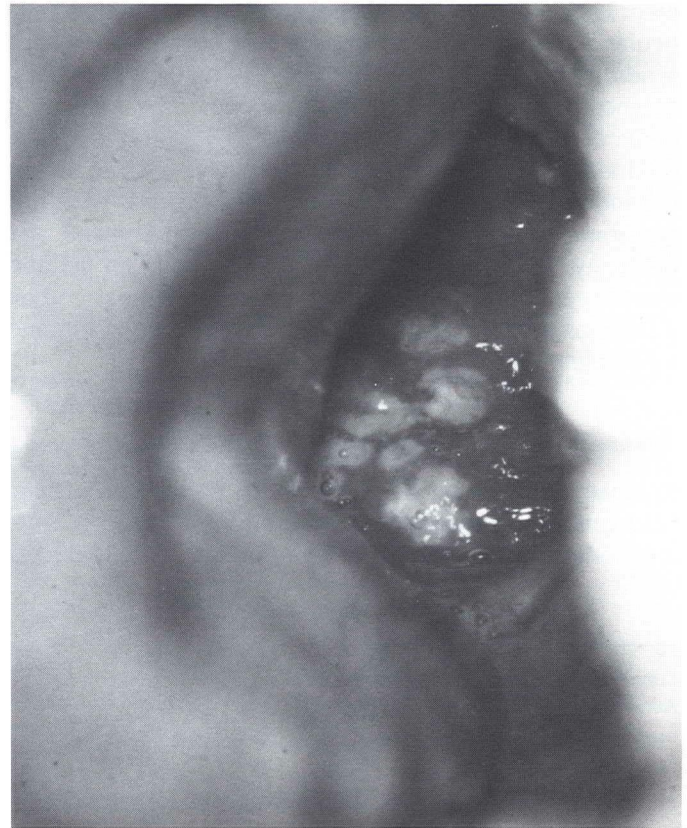


Fig. 1
Ulcers on the palate suggest Behcet's syndrome.



Fig. 2

Skin ulcerations in the peno-scrotal region.

Because we suspected Behcet's syndrome, the patient was hospitalized for further tests. A biopsy from an ulceration of the scrotum revealed that the central portion of the epidermis was completely eroded and the margins were acanthotic. A dense inflammatory infiltrate throughout the dermis was composed of leukocytes, lymphocytes, plasma cells, and histiocytes (Fig. 3). Numerous scattered dilated vessels were seen in the upper dermis. Some vessels in the mid-dermis showed endothelial cell proliferation and an invasion by mononuclear cells. Many vessels were completely occluded. These changes were consistent with the ulcers of Behcet's syndrome. Domeboro compresses were applied to the open lesions along with Lidex in orabase ointment four times a day. Indocin (100 mg daily) was continued. The ulcers completely healed in six days.

Etiopathogenesis

The etiopathogenesis of Behcet's syndrome is complex and intriguing. The cause is still obscure, but a sequence of immunologic events has been implicated, perhaps precipitated by genetic, viral, toxic, and allergic factors.

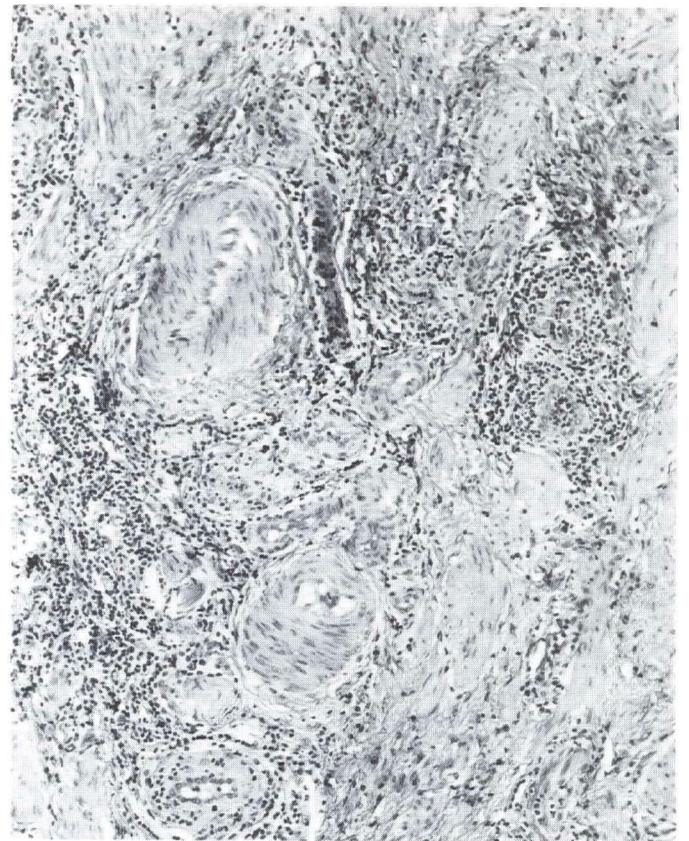


Fig. 3

Penile skin biopsy showing an inflammatory cellular infiltration of mononuclear cells located between the collagen bundles and in close apposition to the blood vessels (H & E 150 X).

Meteorologic factors have also been claimed as a cause, based chiefly on evidence suggesting its greater prevalence in colder climates and the greater frequency of attacks in Japan during the windy season. Hereditary factors are also implicated. The association between the HLA-B5 antigen and Behcet's syndrome is particularly strong in Japan and Turkey, the two countries of greatest prevalence. HLA-A2 and HLA-B27 but not B5 was increased in a series from Yorkshire (U.K.), whereas HLA-B27 was not present in a recent American study of Behcet's syndrome (5,8,9,18-21).

One theory is that Behcet's syndrome is an autoimmune disorder, since a patient's autoreactive antibody against oral mucous membranes has been detected in serum. This belief has been supported by recent immunofluorescence studies demonstrating the deposition of IgM, IgG, and beta 1A globulin in the vessel walls of patients with Behcet's syndrome. The elevated serum complement levels (C1, C4, C2 and C3), raised serum IgG, IgM and IgD, proportionate increase of T lymphocytes and suppression of B lymphocytes in patients with Behcet's syndrome all lend further credibility to the immunologic theory. The report of a macrophage migration inhibitory factor in the anterior

chamber of the eye in Behcet's syndrome suggests that cell-mediated immunity might play a significant role (9).

The immunologic and immunochemical findings in neurological forms of Behcet's syndrome are important. Demyelinating antibodies, similar to those found in multiple sclerosis, are detectable in more than 70% of patients with Behcet's syndrome and neurologic involvement. While the antibodies in multiple sclerosis cause inhibition and destruction of the myelin, those in Behcet's syndrome do not appear to inhibit myelination. Furthermore, an anti-myelin serum factor (AMSF) has been reported recently in the serum and spinal fluid of patients with neuro-Behcet's syndrome during the acute and active phase. A less specific factor known as the cerebroside-binding serum factor (CBSF) has also been detected. The elevation of CSF-IgA, alpha-II macroglobulin, and C3 in patients with neuro-Behcet's syndrome is useful in assessing its severity. These findings seem to support the concept that an immunologic mechanism might play a significant role in the development of the vascular and neurologic manifestations of Behcet's syndrome (7).

The vascular lesions show fragmentation and splitting of the elastic fibers in the media and degeneration of the vasa vasorum associated with perivascular round cell infiltration, while those in the nervous system include the vascular changes described above as well as areas of diffuse demyelination and axonal degeneration.

Clinical Features

Aphthous ulcers

Recurrent aphthous ulcers occur on the mucous membranes of the lips, gingiva, cheeks (buccal mucosa), and tongue. The palate, tonsils, and pharynx are rarely involved. Initially, a red, raised area appears that later becomes a shallow, round, or oval ulcer with erythematous borders. A white or yellowish pseudo-membrane generally covers the surface of this ulcer. Rarely, the ulcers may fuse to form a single large ulcer. Most aphthous ulcers heal without scarring except for those which fuse. In general, these ulcers tend to occur in crops and recur often (9,16).

Skin lesions

Erythema nodosum lesions may occur on the lower extremities and are less commonly seen on the face, neck, and buttocks. The lesion appears as an erythematous, elevated lesion, with subcutaneous induration and tenderness. They tend to recur but are generally self-limiting (2).

Thrombophlebitis in the subcutaneous tissues is known to occur, especially in men, and commonly involves the

subcutaneous venules of the extremities. Less commonly, migrating obliterative thrombophlebitis has been known to occur (23).

Acneiform skin eruptions resembling acne vulgaris appear frequently on the face, neck, breast, and back. Uncharacteristically, some lesions can become pustular, but pruritis is rare (23).

Abnormal hyper-irritability of the skin against nonspecific stimulation is found in 60-70% of patients who have Behcet's syndrome; however, it is not specific for the disorder (10,24,25). In areas where the syndrome is prevalent, a test that uses an aseptic needle to prick the skin can be extremely helpful in diagnosis. The patient will develop a tuberculin-like reaction with erythema and swelling at the injection site 24-48 hours later; aseptic pustules will develop later. The above reaction can be induced by injection of physiologic saline, the patient's saliva, or the aseptic extract of a genital ulcer. Although the mechanism of this phenomenon is not known, it is thought to be related to increased chemotaxis.

Ocular lesions

The most serious problem in Behcet's syndrome is ocular lesions, which involve recurrent episodes of anterior and posterior uveitis sometimes leading to loss of vision. Hypopyon iritis, resulting from anterior uveitis, is a typical, often transient sign, lasting only a few days. Further ocular changes usually follow, with resultant recurrent posterior uveitis, bleeding and exudate formation in the choroid and retina. In a more advanced stage, loss of vision occurs secondary to optic atrophy, glaucoma, and cataract. Very rarely, phthisis bulbae might develop. It usually takes about five years from the onset of ocular symptoms for the patient to lose eyesight completely. Severe ocular involvement seems to be more characteristic of Japanese patients with Behcet's syndrome than of other nationalities (26).

Genital lesions

Aphthous ulcers similar to those in the mouth occur most frequently on the scrotum and vulva and less commonly on the penis, perianal and vaginal mucosa. Genital ulcers are deeper than the oral and may cause scarring. Because the genital lesions in men tend to be more painful, they are more apt to be discovered by the patient. Epididymitis, which is frequently recurrent, has been reported in 4.5-8% of male patients (9).

Articular manifestations

A little over 50% of patients with Behcet's syndrome will develop articular symptoms. The joint involvement is frequently recurrent, asymmetric, and characterized by pain,

redness, and swelling. The knee is the most frequently involved joint, while the ankle, elbow and wrist are less frequently affected. The arthritis is seldom destructive. In contrast to Reiter's syndrome, the sacroiliac joint is seldom involved in Behcet's syndrome. Only 0.5-1% of the Japanese patients showed sacroiliac joint involvement. The rheumatoid factor is negative in almost all cases. Rare cases of erosive arthritis and osteonecrosis of the femur have been documented (23,27-30).

Gastrointestinal and hepatic manifestations

Gastrointestinal symptoms, which may occur in about 50% of patients, include vomiting, abdominal pain, flatulence, diarrhea, and constipation. Malabsorption and maldigestion are common. Ulcerations have been known to occur in the terminal ileum and caecum and could lead to perforation and fissure formation. In general, ulcerative lesions tend to occur more frequently in Japanese patients and carry a poor prognosis. Congestive changes in the liver secondary to occlusion of the hepatic vein (Budd-Chiari syndrome) have also been identified (9,31,32).

Cardiovascular manifestations

Although cardiac involvement is rare, vascular involvement is much more frequent, severe, and can sometimes be fatal. Four types of vascular lesions are recognized: venous occlusions, arterial occlusion, aneurysm, and varices. Vascular symptoms were identified in 7.7% of Japanese patients with Behcet's syndrome during a 1972 nationwide survey. The leading cause of death in Behcet's syndrome in Japan was due to the rupture of a large artery aneurysm (7,11,33). Venous lesions are generally more common than arterial lesions.

Occlusion of the subclavian artery frequently leads to pulseless disease. Aneurysms of the renal artery may lead to hypertension, while peripheral arterial occlusion produces symptoms of intermittent claudication. Cerebrovascular complications secondary to arterial occlusion are well documented (33). Venous occlusions involving the superior or inferior vena cava are frequently observed. The Budd-Chiari syndrome has also been known to occur (34-36).

Arteriography, venography, and thermography have been used to study the different patterns of vascular involvement (37). Generally, it occurs more often in men than in women and is less common when ocular signs are present or permanent (38).

Central nervous system manifestations

Nervous system involvement in Behcet's syndrome, which was first described in 1941, has been well defined and

recognized in Japan. It is usually associated with a poor prognosis. Meningeal disease could mimic the features of microbial meningitis. Vascular occlusions could involve the cerebral or vertebrobasilar circulation, while parenchymatous involvement leading to brain stem, cerebellar, and spinal long tract damage have also been well described. Psychological changes, characterized by amnesia, dementia and personality disturbances, are present in at least 50% of cases (39-42).

Diagnosis and Treatment

The diagnosis of this condition remains syndromic. In addition to the clinical findings, several nonspecific laboratory abnormalities support the diagnosis. These include the increase of serum mucoproteins, reduced albumin, increased globulin, elevated erythrocyte sedimentation rate, increased serum concentrations of IgG, IgM and IgD, elevated serum glycoproteins and sialic acid, leukocytosis, and positive tests for C-reaction protein. In addition, circulating antibodies against human mucosal cells and lymphocytotoxicity to oral epithelial cells have also been found. Most of the abnormalities are detected during the acute attacks and diminish or disappear during remissions (9).

The "needle reaction" is one of the most reliable methods for diagnosis but is unfortunately not present in all patients. Rosettes of platelets around granulocytes may be detectable during the acute phase or during acute attacks and may point to the diagnosis. However, this phenomenon is calcium-dependent and thereby demonstrable only in edetic acid (EDTA) anticoagulated blood (24,25,43).

Differential diagnosis

The most important diseases which mimic some of the mucocutaneous clinical features of Behcet's syndrome include 1) Reiter's syndrome, 2) Stevens-Johnson syndrome, 3) aphthous stomatitis, 4) syphilis, 5) erythema nodosum, and 6) herpetic stomatitis. The joint manifestations should be differentiated from those of Reiter's syndrome.

Reiter's syndrome is characterized by a triad of urethritis, conjunctivitis, and arthritis, as well as by mucocutaneous lesions. The knee is also commonly affected, and the sacroiliac joint and thoracolumbar spine are invariably affected in longstanding cases. Behcet's syndrome is differentiated from Reiter's syndrome by the painful oral and genital ulcerations, recurrent uveitis, and arthralgias rather than arthritis and vasculitis. The lack of sacroiliac joint involvement in Behcet's syndrome is an important point in differentiation.

Clinical course

In the typical case, oral aphthous ulcers appear first, followed by skin lesions, ocular and genital involvement. In

most instances, nervous system and vascular complications occur later. In most patients frequent attacks occur early in the disease followed by a slowing of activity. Eye symptoms tend to become chronic and eventually lead to loss of visual acuity or to blindness.

Men appear to be affected more often than women (ratio 1.2 to 2). However, a female preponderance has been noted in a series reported from the U.S. and the U.K. In general, the younger the patient, the poorer the prognosis. Young men usually have the worst prognosis (8,42,44). The mucocutaneous lesions without ocular involvement are relatively frequent in women over 45; this has been termed the incomplete type of Behcet's syndrome.

Prognostic predictors of Behcet's syndrome are not well delineated. In general, progression of neurologic disease carries a poor prognosis. Death generally results from lesions of the central nervous system or vascular system and from intestinal perforation (9).

Management

The treatment of Behcet's syndrome is controversial and difficult. Some aspects of therapy continue to be empirical and palliative. Transfer factor has been used in some studies and has had moderate-to-great effectiveness in controlling some recalcitrant lesions and in reducing the number of new lesions and new attacks. More recently, immunosuppressive therapy has been recommended, while immunostimulant drugs (e.g., Levamisole) have also been used. Colchicine has been used in some cases, chiefly because of its antichemotactic activity. In the past, fibrinolytic drugs have also been used, chiefly to combat the fibrinolytic deficiency. Corticosteroids have largely been used as a palliative mode of therapy (9).

Discussion

In the U.S., Behcet's syndrome is still considered rather uncommon (5,28), although Duffy, et al (44) believe that the disease usually passes unrecognized and is not that rare. They described clinical and immunologic findings in 10 patients with Behcet's syndrome. Other cases reported in the U.S. include that of a 49-year-old woman with uveitis, recurrent orogenital lesions, polyarthritis, and skin lesions (30); a patient with recurrent pneumonia associated with Behcet's syndrome that occurred over 13 years; a patient with thrombophlebitis, skin lesions, diffuse pulmonary infiltrate, and severe hemoptysis (45); and a patient with Behcet's syndrome and neurologic involvement (22).

Behcet's syndrome is a multisystemic disease. Our patient presented with recurrent aphthous and genital ulceration, two major criteria, and with arthritis that was neither

episodic nor destructive. In the light of a high index of suspicion clinically, these criteria would justify the diagnosis of incomplete Behcet's syndrome, which was consistent with the biopsy findings. His positive HLA-B27 antigen is interesting, although a clear relationship between this factor and Behcet's syndrome remains speculative. Our patient may eventually develop ocular or other manifestations characteristic of this syndrome. As yet, the patient has had no serious problems but eventually he might require the therapeutic agents mentioned. His prognosis therefore remains guarded.

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